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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/694,519	10/23/2000	Robert Joseph Isfort	8311	9641

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EXAMINER
STRZELECKA, TERESA E

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 03/24/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/694,519	ISFORT ET AL.	
	Examiner	Art Unit	
	Teresa E Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *1-14,18-26 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-17 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. Receipt is acknowledged of a request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e) and a submission, filed on January 3, 2003.

2. Claims 1-28 are pending, with claims 1-14, 18-26 and 28 withdrawn from consideration.

Response to Arguments

3. Applicants' arguments filed on January 3, 2003 have been considered.

4. Arguments considering rejection of claims 15-17 and 27 under 35 U.S.C. 112, first paragraph (enablement) will be considered first. Applicants argue the following:

A) The compounds of the invention are specific for VPAC receptors, therefore the side effects should be minimal, therefore no undue experimentation would be necessary (page 2, fourth paragraph).

B) Regarding VIP, PAPAC-27, PVI, GHRH etc., Applicants state the following "Applicants agree that these compounds may act through VPAC receptors at certain concentrations, but these compounds do not exhibit specificity for VPAC receptors. It is well known in the art that these compounds bind other receptors as well (citations omitted) and thus lack specificity for the VPAC receptors. Therefore the use of these promiscuous compounds could lead to toxicity, undesirable side effects, and overall unwanted physiological consequences."

Regarding A and B), Applicants' argument in the last paragraph regarding VIP, PAPAC-27, PVI, GHRH etc. is in fact supporting the enablement rejection. In addition, claim 15 is drawn to any VPAC receptor agonist, not just agonists which are selective for VPAC receptors. Applicants definition of selectivity is (page 12, lines 7-9): ""Selective agonist" means that the agonist has significantly greater activity toward a certain receptor(s) compared with other receptors, not that it

is completely inactive with regard to other receptors." However, Applicants do not define what level of activity is considered to be "significantly greater". Finally, in claim 17 VIP, PAPAC-27, PVI, GHRH, helodermin, etc., are included in the Markush group of selective VPAC agonists.

5. Arguments considering art rejections:

A) Rejection of claims 16, 17 and 27 under 35 U.S.C. 102(b) over Vittone et al. is improper, because the doses administered by Vittone et al. would not act through the VPAC receptors. Applicants cite examiner's argument, brought in the enablement rejection, that GHRH is not specific for the VPAC receptor.

B) Rejection of claim 15 under 35 U.S.C. 102(b) over Gourlet et al. is improper, because examiner's argument of the compound's intended use was applied incorrectly. Applicants cite MPEP 2112.02 in support of the fact that a new and unobvious use of old structures and compounds in patentable.

Regarding A), Applicants do not claim the doses of GHRH which would make it selective for VPAC receptors, and claim 17 lists GHRH as a selective VPAC agonist. Regarding B), Applicants correctly conclude from the cited MPEP paragraph that a new use of an old compound may be patentable. However, claim 15 is not a method claim, but a composition claim, which is drawn to any VPAC receptor agonist and a pharmaceutically acceptable carrier, the two limitations being anticipated by Gourlet et al. The following MPEP paragraphs support this conculsion:

2112.01 Composition, Product, and Apparatus Claims

PRODUCT AND APPARATUS CLAIMS — WHEN THE STRUCTURE RECITED IN THE REFERENCE IS SUBSTANTIALLY IDENTICAL TO THAT OF THE CLAIMS, CLAIMED PROPERTIES OR FUNCTIONS ARE PRESUMED TO BE INHERENT

Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the

applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433. See also Titanium Metals Corp. v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) (Claims were directed to a titanium alloy containing 0.2-0.4% Mo and 0.6-0.9% Ni having corrosion resistance. A Russian article disclosed a titanium alloy containing 0.25% Mo and 0.75% Ni but was silent as to corrosion resistance. The Federal Circuit held that the claim was anticipated because the percentages of Mo and Ni were squarely within the claimed ranges. The court went on to say that it was immaterial what properties.the alloys had or who discovered the properties because the composition is the same and thus must necessarily exhibit the properties.). See also In re Ludtke, 441 F.2d 660, 169 USPQ 563 (CCPA 1971) (Claim 1 was directed to a parachute canopy having concentric circumferential panels radially separated from each other by radially extending tie lines. The panels were separated "such that the critical velocity of each successively larger panel will be less than the critical velocity of the previous panel, whereby said parachute will sequentially open and thus gradually decelerate." The court found that the claim was anticipated by Menget. Menget taught a parachute having three circumferential panels separated by tie lines. The court upheld the rejection finding that applicant had failed to show that Menget did not possess the functional characteristics of the claims.); Northam Warren Corp. v. D. F. Newfield Co., 7 F. Supp. 773, 22 USPQ 313 (E.D.N.Y. 1934) (A patent to a pencil for cleaning fingernails was held invalid because a pencil of the same structure for writing was found in the prior art.).

COMPOSITION CLAIMS - IF THE COMPOSITION IS PHYSICALLY THE SAME, IT MUST HAVE THE SAME PROPERTIES

"Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) (Applicant argued that the claimed composition was a pressure sensitive adhesive containing a tacky polymer while the product of the reference was hard and abrasion resistant. "The Board correctly found that the virtual identity of monomers and procedures sufficed to support a prima facie case of unpatentability of Spada's polymer latexes for lack of novelty.").

6. In view of the above arguments all previous rejections are maintained. New rejections have been added.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 15-17 and 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for VPAC (vasoactive intestinal peptide) receptor agonists specific for either $VPAC_1$ ([K^{15}, R^{16}, L^{27}, VIP(1-7), GRF(8-27)-NH_2]), $VPAC_2$ (Ro 25-1553) or both $VPAC_1$ and $VPAC_2$ receptors (PACAP-38, pituitary adenylate cyclase-activating polypeptide), does not reasonably provide enablement for any other compound or any of the other agonists listed in claim 17. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claim 15 is drawn to a pharmaceutical composition comprising a safe and effective amount of a VPAC receptor agonist and a pharmaceutically acceptable carrier. Claim 27 is drawn to a method of increasing skeletal muscle mass in a subject in which an increase is desirable, by administering to the subject a safe and effective amount of a compound that selectively acts through the VPAC receptor. Therefore claim 27 is drawn to both agonists and antagonists of the VPAC receptors.

Applicants described using the following VPAC receptor agonists to counteract muscle atrophy in mice: [K^{15}, R^{16}, L^{27}, VIP(1-7), GRF(8-27)-NH_2], Ro 25-1553 and PACAP-38. Applicants did not provide an example of even a single VPAC receptor antagonist which induces increase in the skeletal muscle mass (page 15, lines 15-32; page 16 17; page 18, lines 1-13). The specification does not provide any indications that VPAC receptor agonists such as VIP (vasoactive intestinal peptide), PACAP-27, helodermin, peptide histidine isoleucine amide (PHI), peptide histidine methionine amide (PMI), peptide histidine valine amide (PVI), growth hormone releasing hormone (GHRH, GRH, GRF), secretin, glucagon, (Arg15, Arg21) VIP, [Arg 15,20,21, Leu17]-

VIP-Gly-Lys-Arg-NH_2, multimeric VIP fusion protein, Ro-1392 and PACAP(6-38), when administered to a subject, would result in an increase of the skeletal muscle mass or function.

The agonists of VPAC receptors listed above are related to VIP, whose receptors are widely distributed in the central and peripheral nervous system and in plasma membranes of many organs and tissues (gastrointestinal tract, lung, heart, uterus, adrenal, adipocytes, enterocytes, hepatocytes, liver, etc.). VIP has a broad range of biological actions, such as vasodilation of vessels, brochodilation, relaxation of various muscles (esophageal sphincter, fundic muscle, gallbladder smooth muscle, colonic smooth muscle of the intestines), glycogenolysis and lipolysis, bone resorption, release of insulin, glucagon, or somatostatin in the pancreas, stimulation of prolactin, growth hormone (GH) release in the pituitary, etc. (Said, J. Endocrinol. Invest., vol. 9, p. 191-200, 1986).

In addition, helodermin, glucagon, GRF, secretin have their own specific receptors, but also bind to the VIP receptors. For example, secretin, GRF, PHI and helodermin bind to the VIP receptor, VIP, GRF, PHI and helodermin bind to the secretin receptors (in pancreas and exocrine cells), glucagon binds to its receptors in the liver, and GRF to its receptors in the pituitary gland (Laburthe et al., Ann. NY Acad. Sci., vol. 527, pp. 296-313, 1988, see Fig. 9). GRF and PHI were found to be VIP receptor agonists (Emami et al., Peptides, vol. 7, pp. 121-127, 1986, see Abstract), and PHM was found to be a VIP agonist with low potency on human VIP receptors (Laburthe et al., Life Sci., vol. 36, pp. 991-995, see Abstract).

PACAP-38 and PACAP-27 in addition to binding to their own receptors bind to the VIP receptors (Ulrich et al., Gastroenterology, vol. 114, pp. 382-397, 1998, see page 387, third paragraph).

Therefore, taking all of the above facts into account, administration of any of the above VPAC agonists, despite the fact that they are related, cannot be predicted to have an effect of increasing muscle strength or function, and may potentially lead to harmful outcome, as they also target other receptors. As noted by Musso et al. (U.S. Patent No. 4,835, 252): " ...the naturally occurring VIP has so many biological activities that its use is limited, because beneficial effects are associated unavoidably with significant, deletorious side effects, especially when the VIP is administered intravenously..." (col. 2, lines 27-31).

Due to the large quantity of experimentation necessary to establish whether the administration of compounds other than [K^{15}, R^{16}, L^{27}, VIP(1-7), GRF(8-27)-NH_2], Ro 25-1553 and PACAP-38 would result in an increase of muscle mass or function, the lack of direction/guidance presented in the specification regarding administration of compounds other than [K^{15}, R^{16}, L^{27}, VIP(1-7), GRF(8-27)-NH_2], Ro 25-1553 and PACAP-38 resulting in an increase of muscle mass or function, the lack of working examples directed to the administration of compounds other than [K^{15}, R^{16}, L^{27}, VIP(1-7), GRF(8-27)-NH_2], Ro 25-1553 and PACAP-38 and resulting increase of muscle mass or function, the complex nature of the invention (agonist binding to several receptor types), the unpredictability of the effects of the administration of compounds other than [K^{15}, R^{16}, L^{27}, VIP(1-7), GRF(8-27)-NH_2], Ro 25-1553 and PACAP-38 on an increase of muscle mass or function (see discussion above), undue experimentation would be required of the skilled artisan to use the claimed invention in its full scope.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 16, 17 and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 27 is indefinite over the recitation of "... a subject in which an increase in muscle mass is desirable..." (emphasis added). Applicants did not provide a definition of what subjects are classified in this category.

B) Claim 27 is indefinite over the recitation of "... a compound that selectively acts through the VPAC receptor...". It is not clear what compounds are encompassed by the term "selectively acting". Applicants definition of selectivity is (page 12, lines 7-9): ""Selective agonist" means that the agonist has significantly greater activity toward a certain receptor(s) compared with other receptors, not that it is completely inactive with regard to other receptors." However, Applicants do not define what level of activity is considered to be "significantly greater".

C) Claim 16 is indefinite over the recitation of: "... compound is a selective VPAC receptor agonist". It is not clear what VPAC agonists are encompassed by the term "selective". Applicants definition of selectivity is (page 12, lines 7-9): ""Selective agonist" means that the agonist has significantly greater activity toward a certain receptor(s) compared with other receptors, not that it is completely inactive with regard to other receptors." However, Applicants do not define what level of activity is considered to be "significantly greater".

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claim 15 is rejected under 35 U.S.C. 102(b) as being anticipated by Gourlet et al. (WO 98/02453).

Gourlet et al. teach peptides which are highly selective for the VIP1 (=$VPAC_1$) receptor, are agonists or antagonists, and pharmaceutical compositions comprising the peptides and pharmaceutically acceptable carrier (page 4, lines 8-11; page 5, lines 14-29; page 9, lines 17-24).

13. Claims 16, 17 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Vittone et al. (Metabolism, vol. 46, pp. 89-96, 1997).

Vittone et al. teach improved muscle function in elderly men (who suffer from the decrease in muscle mass and strength due to age-related decrease in growth hormone, GH, and insulin-like growth factor-I, IGF-I) after administration of single nightly injections of GHRH (Abstract; page 94, paragraph 4).

14. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (703) 306-5877. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (703) 308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

March 21, 2003

Teresa Strzelecka, Ph. D.

Patent Examiner

Teresa Strzelecka
3/21/03